**Review**

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**Obesity-associated sympathetic overactivity in children and adolescents: the role of catecholamine resistance in lipid metabolism**

DOI 10.1515/jpem-2015-0182
Received May 2, 2015; accepted August 27, 2015

**Abstract**

**Background:** Obesity in children and adolescents is characterized by chronic sympathetic overdrive and reduced epinephrine-stimulated lipolysis. This resistance to catecholamines occurs during the dynamic phase of fat accumulation. This review will focus on the relationship between sympathetic-adrenal activity and lipid metabolism, thereby highlighting the role of catecholamine resistance in the development of childhood obesity.

**Results and conclusions:** Catecholamine resistance causes lipid accumulation in adipose tissue by reducing lipolysis, increasing lipogenesis and impeding free fatty acid (FFA) transportation. Exercise improves catecholamine resistance, as evidenced by attenuated systemic sympathetic activity, reduced circulating catecholamine levels and enhanced β-adrenergic receptor signaling. Insulin resistance is mostly a casual result rather than a cause of childhood obesity. Therefore, catecholamine resistance in childhood obesity may promote insulin signaling in adipose tissue, thereby increasing lipogenesis. This review outlines a series of evidence for the role of catecholamine resistance as an upstream mechanism leading to childhood obesity.

**Keywords:** catecholamine resistance; childhood obesity; insulin resistance; lipid metabolism; sympathetic activity.

**Introduction**

Obesity is a health hazard that is characterized by increased lipogenesis and excess energy storage in the adipose tissue depots. White adipose tissue (WAT) is a specialized lipid storage organ that stores energy as triglyceride-enriched lipid droplets. Brown adipose tissue (BAT) converts excess fat into heat via uncoupled respiration, which is dependent on sympathetic nerve activation. At synapses within the sympathetic ganglia, preganglionic sympathetic neurons release acetylcholine, a chemical messenger that binds and activates nicotinic acetylcholine receptors on postganglionic neurons. In response to this stimulus, postganglionic neurons release noradrenaline, which binds adrenergic receptors on the target tissues and cells and thus causes the downstream effects (known as the fight-or-flight response). The adrenergic receptors (AR) are G protein-coupled receptors that are targets of catecholamines, including norepinephrine (NE, noradrenaline) and epinephrine (adrenaline). Sympathetic stimulation causes various responses in different organs and tissues directly depending on the alpha subunit type of G-protein. In adipose tissue, sympathetic nerve activity (SNA) enhances lipolysis and thermogenesis due to increased function of β3-ARs (major finding), decreased function of a2-ARs and increased ability of cyclic AMP to stimulate lipolysis. Thus, catecholamine may prevent obesity, especially in subjects with aging and diabetes (1). Adrenal secretion of epinephrine is reduced in obese adults with different manifestations of metabolic syndrome (2). In this regard, lower SNA contributes to the development of obesity (3). SNA prevents insulin-induced fatty acid synthesis and lipogenesis, resulting in atypical insulin resistance in adipose tissue. Thus, β3-AR agonist (Ractopamine, Clenbuterol, etc.) has potential to treat obesity through modulation of lipolysis (4).

However, SNA is really enhanced in some obese humans, especially in subjects who are young and healthy.
(5). Sympathetic overactivity occurs in obese animals, as evidenced by increased blood pressure, cardiac output, heart rate as well as the activation of renin-angiotensin-aldosterone system (6). Obesity-related hypertension in pediatric patients is a consequence of the childhood obesity with the activation of the renin-angiotensin-aldosterone system (RAAS) and the stimulation of sympathetic nervous system (7). Significantly, adipose tissue lipolysis shows a decreased sensitivity to epinephrine in childhood obesity. This resistance to catecholamines occurs during the dynamic phase of fat accumulation, suggesting that epinephrine resistance might be the cause rather than the result of childhood obesity (8, 9). These studies demonstrate that SNA is really impaired in obese people especially in children and adolescents. This review will focus on the correlation between sympathetic nerve system (SNS) and childhood obesity. Here, we propose a potential link between catecholamine resistance and lipid metabolism in the progression from sympathetic overdrive to impaired catecholamine sensitivity and obesity.

**Psychosocial stress, sympathetic activity and childhood obesity**

Psychosocial stress has become another contributor to the development and maintenance of obesity in children and adolescents except high-fat diet and physical inactivity (10, 11). Chronic psychosocial stress, combined with a high-fat/high-sugar diet, has been shown to activate SNS and accelerate diet-induced obesity and the metabolic syndrome (12). An interesting study shows that social overcrowding is a chronic stress that increases adiposity in mice (13). Prenatal and postnatal exposure to a high-fat diet elevates SNA and arterial pressure in rabbits (14, 15). Social defeat stress activates thermoregulatory sympathetic premotor neurons (16). Chronic social stress increases sympathetic-adrenal-medullary axis activity in mice (17) and enhances sympathetic innervation of primate lymph nodes (18). Clearly, chronic exposure to either high-fat diet or social stress stimulates SNS and further leads to chronic and low grade sympathetic activity. Chronic sympathetic activation contributes to the development of hypertension and the metabolic syndrome by impairing beta-adrenergic signaling and insulin sensitivity (19). In obese humans and animals, elevating circulating leptin levels in turn activate SNA (20). Thus, chronic sympathetic overactivity in obesity creates a vicious circle that deteriorates insulin resistance and leptin resistance (Figure 1). In addition, sympathetic activation may increase adrenal secretion, thus sympathetic-adrenal system (SAS) constitutes a key neuroendocrine pathway to modulate lipid metabolism.

The earlier studies reported that NE infusion-induced thermogenesis and vascular pressure elevation were greater in the younger rats compared to the older rats (21, 22). We think that these results do not conflict with the hypothesis of catecholamine resistance presented in this review, because obesity was not involved in these studies. These findings only suggest that the younger rat has greater NE sensitivity than the older. Contrary to earlier experimental evidence, human obesity is characterized by sympathetic nervous activation, with the outflows to both the kidney and skeletal muscle being activated (23). Indeed, many recent studies report increased SNA and decreased catecholamine sensitivity in obese individuals. Muscle SNA was clearly elevated in nondiabetic obese patients, whose weight loss was associated with the decrease in SNA and blood pressure (24). Excessive renal sympathetic nerve activation underlies obesity-related hypertension (25). A 5-year longitudinal study in young, nonobese, normotensive men demonstrates that increase in plasma NE levels precedes subsequent weight gain and blood pressure elevation (26). Increasing data suggest the relationship between the development of obesity and SNA as indicated by the following observations: regional activation of SNS in obese normotensive human subjects (27), adrenergic overdrive in obese normotensive individuals with obstructive sleep apnoea (28), enhanced sympathetic neural drive associated with visceral obesity (29), reduced SNA associated with the beneficial effects of exercise (30), and an association between weight gain and increasing SNA (31), etc. Importantly, the activation of SAS and SNS is known as a major cause of obesity-induced hypertension (6). Hypertension with childhood obesity indicates that cardiovascular system may be sensitive to SNA, whereas adipose tissues lipid metabolism is resistant or insensitive to SNA.

If sympathetic overactivity causes childhood obesity, can beta-blockade reduce the sympathetic overactivity and restore the energy imbalance? Sympathetic activation reduces serum adiponectin levels and adiponectin synthesis in WATs, thereby promoting the development of the metabolic syndrome. In subcutaneous, epididymal, and mesenteric fat tissues, these effects on adiponectin and uncoupling protein 1 (UCP1) expressions were reversed by β3 blocker SR59230A and propranolol (32). Propranolol also increased lipid oxidation, which was more significant in more obese subjects with a higher basal SNA. β2-adrenoreceptor blockade (ICI-118551) reduces the early post trauma hyperglycemia in obese rats (33). From these
In early studies, it was hypothesized that beta-blockade improves metabolism in the subjects with higher SNA. Really, beta-blockers are effective for children and adolescents with hypertension (34). Unfortunately, chronic beta-blockade causes obesity by blunting energy expenditure (35). Beta-blockers are different in their effects on glucose and lipid metabolism. Traditional beta-blockers cause insulin resistance and dyslipidemia because cardiac output decreases and peripheral vascular resistance increases or remains unchanged. Vasodilating beta-blockers reduce peripheral vascular resistance rather than cardiac output; therefore, they have less impact on insulin sensitivity and glycemic control than traditional beta-blockers (36). Additionally, heart rate variability during childhood (from high to low) is caused by a progressive increase in parasympathetic activity relative to sympathetic activity. Obesity can disrupt cardiac autonomic control (37). Lower parasympathetic activity is a significant risk factor for the development of pediatric obesity (38). Obese children are characterized by cardiovascular autonomic dysfunction and increased leptin, insulin resistance (39). It is currently unclear whether lower parasympathetic activity is more important for the development of children obesity than sympathetic overactivity, and whether such sympathetic overactivity in childhood obesity comes at the expense of lower parasympathetic activity. It has been fully established that childhood obesity is mostly featured by sympathetic overactivity, and lipolysis in adipocytes shows a resistance to SNA and catecholamines. We define the reduced sensitivity to catecholamine in adipose tissue as catecholamine resistance.

**Figure 1:** Chronic sympathetic overactivity creates a vicious circle that deteriorates insulin resistance and leptin resistance in obesity. Chronic social stress, combined with a high-fat diet, has been shown to activate sympathetic nerve system (SNS) and elevate plasma glucose levels. In the early phase of obesity, increasing plasma glucose induces insulin secretion from islet beta-cells, whereas sympathetic activation is able to suppress insulin secretion. On the other hand, chronic sympathetic activity stimulates epinephrine secretion from adrenal medulla, resulting in increased circulating catecholamine levels. Catecholamine resistance in adipose tissue increases lipid accumulation by reducing lipolysis and promoting lipogenesis. Lipid accumulation causes insulin resistance and obesity increases leptin, resistin and visfatin synthesis, thus leading to the first vicious circle: obesity-leptin secretion↑-adipose tissue leptin resistance-obesity↑ (A). In addition, elevating circulating leptin levels further activate sympathetic activity, thereby creating the second vicious circle: SNS-epinephrine↑-adipose tissue catecholamine resistance-obesity-leptin↑/resistin↑ /adiponectin↓-SNS↑ (B). In the obese phase, the reduction of systemic catecholamine sensitivity leads to the inability of SNS to suppress insulin secretion, thereby increasing plasma insulin and creating the third vicious circle: insulin secretion↑-insulin resistance-obesity↑-leptin↑-SNS↑- pancreas catecholamine resistance-insulin secretion↑↑ (C).
**Sympathetic activity, adipokine and childhood obesity**

Recent studies in understanding childhood obesity show the emerging role of the adipokines leptin, adiponectin, resistin, and visfatin in the pathophysiology of obesity. The deregulation of serum adipokine levels is linked to the overactivity of sympathetic and renin-angiotensin-aldosterone systems (40). Further, the dysregulated production of adipokines seen in obesity contributes to the development of metabolic and cardiovascular diseases (41).

First of all, leptin levels are significantly elevated in obese children (42, 43). This elevated leptin concentration causes an increase in thermogenesis through increased SNA to BAT (44). Leptin also causes sympathetic excitation to the kidney that, in turn, increases arterial pressure. Moreover, diet-induced obesity in mice shows a preserved arterial pressure response to leptin despite the resistance to the metabolic action of leptin (20), suggesting that SNS subserving different tissues is differentially controlled by leptin. For instance, PI3K and melanocortin receptors mediate leptin-induced renal sympathetic activation in obesity (45). The stimulatory effects of leptin on the SNS are enhanced by oestrogen, via an increase in alphamelanocyte-stimulating hormone activity in the paraventricular nucleus of the hypothalamus (46).

Second, resistin levels show a positive correlation with fat mass in children, particularly in girls (47). The resistin levels were higher in obese Chinese children compared to healthy children, and it is positively correlated with BMI, waist circumference, systolic blood pressure, fasting insulin, etc. (48). Further, central resistin enhances renal and lumbar SNA but reduces the SNA to BAT (49, 50). The findings indicate that resistin differentially regulates SNA to different tissues involved in metabolic and cardiovascular regulation. In addition, another adipokine visfatin is also markedly elevated in obese children (51–53). It remains unclear whether and how visfatin regulates SNA.

Conversely, adiponectin levels are lower in childhood obesity and increase with decreasing body weight (54). Adiponectin can decrease renal sympathetic activation and blood pressure in a dose-dependent manner (55). Sympathetic activation reduces serum adiponectin levels and adiponectin expression in WATs in vivo, although responsiveness to SNS stimulation differs markedly among WATs (32). In summary, the adipokines elevated by obesity appears to increase renal sympathetic activation and thereby causes hypertension, while the adipokines repressed by obesity appears to decrease sympathetic activation and thus relieves hypertension and increases insulin sensitivity (56, 57). Obesity-related dysregulation of adipokine endocrine may further increase SNA, thereby aggravating the vicious circle in the neuro-endocrine-adipocrine axis (Figure 1). It is currently unclear why obesity-derived WAT cannot increase the adiponectin endocrine, and why the SNA to adipose tissues is blunted at obese state.

**Catecholamine resistance and lipid metabolism**

**Lipolysis and catecholamine resistance**

Lipolysis is the breakdown of lipids and involves hydrolysis of triglycerides into glycerol and free fatty acids. Hormone-sensitive lipase (HSL) is an intracellular neutral lipase that is capable of hydrolyzing a variety of esters: triglyceride, diglyceride, monoglyceride, and cholesteryl ester. Adipose triglyceride lipase (ATGL) is another important triacylglycerol hydrolase in adipose and nonadipose tissues. The efficient ATGL enzyme activity requires activation by comparative gene identification 58 (CGI-58). Catecholamines, glucagon and adrenocorticotropic hormone (ACTH) can stimulate HSL and ATGL via beta-adrenergic signaling, providing major source of energy for most cells. β-Adrenoreceptors mediate a series of intracellular events and the activation of lipolysis following catecholamine binding. A series of studies show that high-fat diet significantly reduces β3-AR expression in adipose tissue (58, 59), and that low-protein, high-carbohydrate diet decreases β3-AR content in brown adipose tissue of rats (60). On the other hand, an antiobesity prescription of Chinese medicine increases β3-AR expression in perirenal fat tissue and reduces body weight, wet weight of visceral fat, and diameter of adipocytes (61). A VGF-derived peptide, TLQP-21, can increase energy expenditure and prevent the early phase of diet-induced obesity by the upregulation of β2-AR, β3-AR and UCP1 (62). Therefore, a negative correlation has been found between obesity and β3-AR activity in adipose tissue. Catecholamine resistance is at least partly associated with a reduction of β3-AR in adipose tissue after high-fat feeding.

G proteins are coupled with β-adrenoreceptors and involved in transmitting signals from a variety of stimuli outside a cell into the inside of the cell. G protein complexes are made up of α, β and γ subunits. The catecholamine activates CAMP-dependent pathway by stimulating the subtype Gαs and adenylate cyclase (AC). On the contrary,
the subtype \( G_{\alpha i} \) inhibits the production of cAMP from ATP, thereby producing antagonistic effects of catecholamine. An exciting study show that \( G_{\alpha i} \)-(G184S) knock-in mice are resistant to weight gain, have decreased body fat, and are protected from insulin resistance on a high-fat diet (63). This result suggests that inactivation of \( G_{\alpha i} \) appears to enhance adipocyte sensitivity to catecholamine so as to increase energy expenditure. Early in 1995, adipocyte plasma membranes from obese patients were found to be less responsive to isoproterenol than those from normal-weight subjects. The response was correlated negatively with fat cell size and positively with \( \beta \)-adrenoreceptor density and with the ratio of beta-receptors and \( G_{\alpha i} \) (64). Thus, catecholamine sensitivity in vivo determines the lipid metabolic consequences associated with obesity.

Adenylate cyclase (AC) catalyzes the conversion of ATP to cAMP and pyrophosphate. The cAMP produced by AC then serves as a regulatory signal to stimulate intracellular lipolysis via specific cAMP-binding proteins (e.g. cAMP-dependent kinase, PKA). AC3−/− mice exhibit obesity. Before the onset of obesity, young AC3−/− mice have exhibited physical inactivity, increased food uptake, and leptin insensitivity (65). It suggests that cAMP signals generated by catecholamine and SNS may play a critical role in the development of obesity. Further, agmatine protects against high fat diet-induced obesity by elevating the synthesis and levels of cAMP and increasing \( \beta \)-oxidation (66). In vitro study indicates that long-term leptin treatment reduces AC activity and cell responsiveness to catecholamines (67). On the basis of the above, elevated leptin concentrations in obese subjects may further reduce tissue responsiveness to catecholamines by reducing AC activity (68). Increased SNS activity and elevated leptin levels in children with metabolic syndrome suggest that leptin-induced reduction of AC activity may lead to catecholamine resistance and childhood obesity (69). In diet-induced obesity, cardiac AC response to fluoride or forskolin (AC agonists) is impaired and \( \beta \)-ARs are suppressed in cardiac muscle and cerebellum (70). Obesity decreases beta-Adrenergic stimulation of adenylyl cyclase by 75% in WAT and by 90% in BAT. High-fat diet markedly blunts beta-agonist-stimulated adenylyl cyclase in BAT (4), indicating a significant retention of beta-Adrenergic stimulation in adipose tissue.

Protein kinase A (PKA), cAMP-dependent protein kinase, acts to phosphorylate acetyl-CoA carboxylase (ACC) and pyruvate dehydrogenase (PDH), thus inhibiting lipogenesis and promoting net gluconeogenesis. On the other hand, PKA phosphorylates HSL and ATGL, thus stimulating lipolysis. In Cushing syndrome, increased PKA activity in adipose tissue is associated with lower BMI. The observed correlation is in agreement with the known roles of PKA in lipolysis (71). Interestingly, knockout of the regulatory subunits RIIa, IIb or the catalytic subunit Cbeta of PKA leads to a lean phenotype in mice that resists diet-induced obesity (72, 73). Suppose that these deficiencies in PKA subunits may increase PKA activity and lipolysis, however, high-fat diet did not suppress PKA activity in liver, skeletal muscle, and WAT (74), but strongly reduced HSL phosphorylation at Ser660 (75). Thus, we propose that PKA-dependent HSL phosphorylation is not required for lipolysis. In HFD-induced subcutaneous adipose tissue, AC activator forskolin activates lipolysis independent of HSL phosphorylation (76).

In addition to HSL phosphorylation, HSL activity is probably regulated by its intracellular redistribution (77). In skeletal muscle, epinephrine or muscle contraction stimulates HSL translocation to intracellular lipid droplet and hydrolyzes triglyceride (78). In cooperation with HSL translocation, a lipid droplet surface protein (perilipin) regulates lipolysis by protecting or exposing the triacylglycerol core of lipid droplet to lipases (79). Of the protein family of perilipins, perilipin 1 potently suppresses basal lipolysis in adipocytes, whereas perilipins 2 and 3 facilitate higher rates of basal lipolysis in other tissues (80). Perilipin expression in human adipose tissue is elevated with obesity (81). High-fat diet increases the expression level of perilipin 5 and leads to a great increase in muscular triglyceride concentration (82). Importantly, perilipin 1 overexpression in adipose tissue dramatically inhibits catecholamine-stimulated lipolysis (83). Thus, obesity-induced perilipin expression impairs catecholamine sensitivity, thus reducing lipid mobilization (Figure 2).

**Lipogenesis, adipogenesis and catecholamine resistance**

Lipogenesis should not be confused with adipogenesis. Lipogenesis encompasses both the process of long-chain fatty acid synthesis and triglyceride synthesis. Adipogenesis is the process of fat cell differentiation regulated by a complex network of transcription factors. At metabolic level, obesity is determined by the balance between lipogenesis and lipolysis. At molecular and cellular level, obesity is determined by the balance between adipocyte proliferation and apoptosis.

Acetyl-CoA carboxylase (ACC) catalyzes the irreversible carboxylation of acetyl-CoA to produce malonyl-CoA, the rate-limiting step in fatty acid synthesis. Acc2−/− mice are protected against fatty liver, obesity and diabetes under high-fat/high-carbohydrate diets (84, 85). Fasting,

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catecholamine and glucagon inhibit ACC activity and reduce fatty acid synthesis. Refeeding and insulin activate ACC activity and increase fatty acid synthesis. ACC activity is controlled by its phosphorylation state. Further, β-adrenergic antagonist (propranolol) or AMPK inhibitor (Compound C) suppresses ACC Ser-79 phosphorylation in abdominal fat. Epinephrine increases ACC phosphorylation mediated through β-AR and AMPK. ACC phosphorylation leads to ACC inactivation, thus reducing fatty acid synthesis and abdominal visceral fat accumulation (86). In a separate study, epinephrine activates AMPK and increases β-oxidation in adipose tissue. However, high-fat diet strongly inhibits epinephrine-induced AMPK activation as well as PGC-1α expression, citrate synthase activity, and palmitate oxidation in epididymal and inguinal fat depots (76). This gives a strong support to the view that high-fat diet impairs adipose tissue epinephrine sensitivity.

The stimulation of cAMP/PKA signaling activates HSL and perilipin, leading to conformational changes and HSL translocation, which facilitate the exposure of lipid droplets to endogenous lipases. Lipolysis alone, however, is not enough to regulate lipid homeostasis. CREB (cAMP response element-binding protein) is a nuclear transcription factor regulated by PKA and protein phosphatase (PP-1). CREB is activated when phosphorylated at Ser-133. In hepatocytes, β-AR/cAMP/PKA/CREB pathway inhibits lipogenesis through the key transcription factors PPARα and hepatocyte nuclear factor 4α (87). Furthermore,
CREB induces expression of the gluconeogenic programme through the nuclear receptor coactivator PGC-1 (88). CREB may suppress expression of the lipogenic programme through the nuclear hormone receptor PPAR-γ because CREB deficiency leads to fatty liver in mice and increases expression of PPAR-γ, a master regulator of lipogenic genes (89). In adipocytes, inhibition of PP1/2A suppresses the progression of adipogenesis by preventing PP1/2A-mediated dephosphorylation of CREB. These results indicate that PKA/CREB phosphorylation is critical for CREB-dependent suppression of adipogenic genes (90). High-fat diet, known as the most important obesity inducer, reduces CREB phosphorylation (91) and epinephrine increases CREB phosphorylation in old rats (92). This provides an interesting possibility for the implications of epinephrine resistance in diet-induced obesity (Figure 2).

**Fatty acid transport and catecholamine resistance**

Dysregulation of FFA transport directly induces ectopic lipid accumulation, which is strongly associated with obesity, fatty liver and metabolic syndrome. In one hand, catecholamine intensively stimulates the release of glycerol and FFA from adipose tissues through cAMP-dependent lipolysis (79, 93). The previous studies have shown that high-fat diet and obesity reduce β-ARs expression and HSL phosphorylation, thereby decreasing the release of FFA from fat tissues. On the other hand, epinephrine induces the expression of myonectin, a novel myokine that is expressed by skeletal muscle and promotes FFA uptake in adipocytes and hepatocytes. In mice, recombinant myonectin administration reduces circulating levels of FFA without altering adipose tissue lipolysis. High-fat diet reduces mRNA and circulating levels of myonectin, whereas voluntary exercise increases its expression and circulating levels (94). These findings provide a novel pathway by which epinephrine promotes FFA uptake in liver and adipose tissue.

For the regulation of FFA transport, catecholamine and glucagon antagonize insulin action, partly because beta-adrenergic stimulation decreases IRS-1 binding to phosphatidylinositol 3-kinase (PI3K) and activation of protein kinase B (95). PI3K inhibitor reduces glucose incorporation into glycereide-glycerol and increases the epinephrine-induced release of FFA from the adipose tissue (96). This suggests that inhibiting insulin signaling enhances adipocyte sensitivity to lipolytic effect. Further evidence in support of the antagonistic role of epinephrine in insulin signaling is provided by studies showing that PKA promotes phosphorylation of IRS-1 and GAB2, adaptors that normally integrate insulin receptor tyrosine kinase signaling into PI3K/Akt (97). These data lead to an alternative hypothesis that epinephrine controls two opposite processes (FFA release and uptake) via two different pathways: cAMP-dependent lipolysis; myonectin-and insulin-mediated FFA uptake (Figure 2).

Therefore, epinephrine resistance in adipose tissue may impair FFA release from adipocytes and epinephrine resistance in skeletal muscle may impair FFA uptake in adipocytes due to reduced expression of myonectin. In diet-induced obesity, epinephrine sensitivity was attenuated in adipose tissue and skeletal muscle (76, 98). Interestingly, insulin resistance is not always associated with obesity and lipid accumulation. Lipatrophy can also result in insulin resistance and metabolic disorders in mice and humans with markedly reduced body fat (99, 100). Lessons from lipoatrophy indicate that epinephrine sensitivity is critical for lipid homeostasis because epinephrine controls the balance of lipid release and uptake.

**Insulin resistance and catecholamine resistance: casual or causal relationship?**

Obesity is strongly associated with insulin resistance and leptin resistance, and childhood obesity is particularly associated with catecholamine resistance. Is obesity the cause or the result of these resistances? This question has never been substantiated. Leptin is mainly produced by adipocytes. Increased adipose tissue induces a higher synthesis and secretion of leptin in obese animals and humans. Therefore, leptin resistance is mostly the result of obesity (101). A longitudinal study in mice under different states of adiposity indicates that leptin resistance is present only when mice are obese. This strongly suggests that leptin resistance is a secondary consequence of obesity (102). Insulin resistance reduces glucose and FFA uptake in peripheral tissues, whereas insulin stimulates anabolism, such as fatty acid synthesis and lipogenesis. The obesity-associated lipid accumulation should not be the result of insulin resistance, but the result of insulin action. Insulin resistance has been observed in adipocytes of nonobese subjects (103). Insulin resistance could be only a casual complication, not the causal factor, in diet-induced obesity.

The earlier studies have shown that exogenous epinephrine treatment induces insulin resistance (104, 105),
whereas endogenous epinephrine protects against obesity-induced insulin resistance (1). These data show that catecholamine regulates insulin sensitivity at upstream. Catecholamine-stimulated PKA increases phosphorylation of IRS-1 and GAB2, thus antagonizing insulin action (97). This is a novel intracellular link in support of the view that catecholamine resists insulin signaling (Figure 2). Obviously, the inhibitory effect of SNS and SAS on insulin signaling must be dependent on the intact catecholamine sensitivity of adipocytes. In this review, I have shown that obesity and high-fat diet attenuate the expression of β3-AR and AC response to beta-Adrenergic stimulation, as well as epinephrine-induced lipolysis, AMPK activation, CREB phosphorylation, and FFA transport (Figure 2). In the adipocytes, the resistance to catecholamine might impair its ability to suppress insulin signaling, thus enhancing insulin-mediated lipogenesis. Especially, SNS and SAS overactivity are present in obese children and adolescents, who are yet in wellness and free of insulin resistance-related complications such as type 2 diabetes. They are obese, but metabolically healthy. Therefore, adipogenesis in childhood obesity should be distinctive. Insulin infused into the mediobasal hypothalamus of rats increases WAT lipogenic protein expression, inactivates HSL, and suppresses lipolysis (106). BAT maintains a significant rate of lipogenesis in the absence of sympathetic activation, but not in the absence of insulin (107). Insulin sensitivity in the fat is specially enhanced in some obese mice (108, 109). Further, we propose that childhood obesity should not be caused by insulin resistance, but by the inability of catecholamine to inhibit insulin action. In contrast to the current dogma, it is elevated insulin signaling in the fat that leads to lipogenesis and childhood obesity. High-fat diet and stress induce chronic SNS activation. As a result, the catecholamine resistance promotes the progression of lipid accumulation at the upstream of insulin signaling (Figure 2).

**Exercise and catecholamine resistance**

Exercise can improve catecholamine resistance. Acute exercise really activates SNS and SAS, and increases the adrenal secretion of catecholamine, but regular exercise decreases SNA in skeletal muscle and cardiovascular system. This improvement in the basal SNS activity is beneficial for hypertension and higher muscle tension in women with polycystic ovary syndrome (110). Exercise training, not acute exercise, reduces circulating catecholamine levels in rats with myocardial infarction, thereby improving sympathetic overdrive and preventing the worsening of the failing heart (111). In chronic heart failure patients, exercise training also prevents the deterioration in the arterial baroreflex caused by SNA (112). Aerobic exercise increases β3-AR expression and restores β3-AR/β1-AR balance, thereby inhibiting cardiac SNA after myocardial infarction (113). This improvement in systemic SNS activity with exercise suggests its potential role in preventing childhood obesity. It is noteworthy that acute exercise-induced sympathetic activation is different from obesity-associated sympathetic overactivity. The former is acute, high grade and transient, but the latter is chronic, low grade and continuous. During exercise-induced sympathetic activation, insulin secretion and lipogenesis are potently suppressed. However, obesity-associated sympathetic overactivity could not suppress insulin secretion and lipogenesis, probably due to the presence of catecholamine resistance in pancreas and fat tissue. In adipose tissue, chronic exercise promotes the expression and phosphorylation of proteins with roles in beta-adrenergic signaling, including β3-AR, ATGL, HSL, CGI-58, and GLUT4 (114, 115). Chronic exercise increases AMPK activity and ACC phosphorylation in WAT (116) and elevates PGC-1α expression and CREB phosphorylation in skeletal muscle (117). These improvements in beta-adrenergic signaling and AMPK signaling suggest that chronic exercise may sensitize lipolytic and lipogenic response to catecholamine in adipose tissue and skeletal muscle. Compared with high-fat diet and chronic social stress, regular exercise decreases the basal level of systemic SNA and circulating catecholamine levels.

Catecholamine signaling involves a variety of adrenergic receptors mediating SNS and endocrine regulation in adipocytes. Exercise has always been thought to activate lipolysis and increase lipid oxidation in the treatment of obesity. However, a shocking study has shown that acute aerobic exercise, which dramatically stimulated adrenergic receptors, induces desensitization in β1- and β2-adrenergic lipolytic pathways in subcutaneous adipose tissue (118). This suggests that lipolysis is inhibited in adipose tissue during exercise. In contrast to β receptors, α2-adrenergic receptor stimulation blunts lipid mobilization in adipose tissue during the activation of SNS. Low calorie diet inhibits α2-receptor-mediated antilipolytic action and reduces its expression (119). In obese human, physiological stimulation of α2-receptor during exercise impairs lipolysis in fat depots (120). Dose it suggests that exercise is harmful to obese human? Another study indicates that chronic exercise reduces acute exercise-induced catecholamine release, thereby preventing the
antilipolytic action of catecholamines mediated by \( \alpha_2 \)-receptor (121). These findings suggest that \( \alpha_2 \)-receptor has a lower sensitivity to catecholamines than \( \beta \)-receptor. Whether exercise activates lipolysis is determined by the selective activation of adrenergic receptors. Chronic sympathetic overactivity in obese children may cause either \( \beta \)-receptors desensitization or \( \alpha_2 \)-receptor-mediated antilipolytic action, thereby reducing lipid mobilization. Anyway, regular exercise attenuates the basal level of SNA and its response to acute exercise, so physical activity is beneficial to lipolysis.

The adipokines leptin, resistin and adiponectin have been show to modulate SNA in childhood obesity. Regular exercise reduced leptin and resistin levels in plasma and increased adiponectin levels in the treatment of obesity (54, 122). In addition, exercise program used in obese middle-aged women was found to reduce visfatin levels (123). Insulin in the brain increases lumbar SNA and baroreflex function in rats (124). Omega-3 fatty acid augments sympathetic outflow to physiological stressors (125). It is well known that exercise reduces plasma levels of insulin and free fatty acid in obese humans and animals. All in all, the plasma parameters that stimulate SNS usually decrease following regular exercise, suggesting that obesity-associated sympathetic overactivity is caused by the dysregulation of these parameters.

**Conclusions**

Sympathetic overdrive is an especial symptom associated with childhood obesity. A combination of high-fat diet and chronic psychosocial stress induces chronic sympathetic overactivity and the consequent catecholamine resistance. Obesity-related sympathetic overactivity is associated with the dysregulation of adipokines and insulin in plasma. In diet-induced obesity, catecholamine resistance could reduce lipolysis, increase lipogenesis and impede FFA transport. Catecholamine resistance may be the upstream cause of childhood obesity relative to insulin resistance. Insulin resistance is not always associated with obesity, so it is only a casual complication with childhood obesity. Catecholamine resistance in adipose tissue may promote insulin signaling, instead of insulin resistance, thus leading to lipid accumulation in the early phase of obesity. However, many questions regarding the nature of catecholamine resistance remain unclear.

Further studies are needed to quantitatively evaluate catecholamine sensitivity in the whole body and adipose tissue during the dynamic phase of lipid accumulation, and to better understand how catecholamine interacts with insulin signaling.

**Acknowledgments:** This work was supported by grants from the National Natural Science Foundation of China (No. 31171142, 31300977), and the Key Laboratory Construction Project of Adolescent Health Assessment and Exercise Intervention of Ministry of Education, China (No. 40500-541235-14203/004).

**Author contributions:** All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

**Research funding:** None declared.

**Employment or leadership:** None declared.

**Honorarium:** None declared.

**Competing interests:** The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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